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10/532,067	12/28/2005	Gerd Sutter	GRUE-004	6100
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EXAMINER				
HURT, SHARON L				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/532,067

Applicant(s)

SUTTER ET AL.

Examiner

SHARON HURT

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2009.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 6-25 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1,2 and 6-25 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 19 April 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/S508)
Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 23, 2009 has been entered.

Response to Amendment

The amendments to the claims filed April 23, 2009 have been acknowledged and entered. New claims 22-25 have been added.

Status of the Claims

Claims 1-2 and 6-25 are pending and under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 103

The rejection of claims 1-2 and 6-21 under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (Vaccine, 1997, Vol. 15, No. 12/13, pages 1303-1313) in view of Kumar et al. (Immunology Letters, April 2002, Vol. 81, pages 13-24) and Bujard et al. (WO 98/14583, 1998) is withdrawn pursuant Applicants arguments.

Claim Objections

Claim 19 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 19 is directed to “the MVA-based virus is MVA”, however the claim is not further limiting from the dependent claim because MVA is MVA-based virus.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 6-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a *Plasmodium falciparum* MSP-1 protein reduced in AT content compared to the wild type sequence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice ... reduction to drawings or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

It is also noted that even the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. See, *In re Smyth*, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in the performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, at 1405 (Fed Cir 1997) (citing *Smyth* for support). Thus, when a claim covers a genus of inventions, the specification must provide sufficient written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed, or provided a function and a structure correlating with that function. However, in situations where the operability of other species than those provided is uncertain, additional support may be required over that which would be required where greater certainty is present.

Claims 20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant application, the claims are drawn to a vaccine composition that does not comprise an adjuvant. Applicant's disclosure lacks written description for a vaccine composition against malaria that does not comprise an adjuvant. In addition, Applicants have introduced **new matter** in the new claims added 6/27/2008 and 4/23/2009 by adding "wherein the vaccine does not comprise an adjuvant".

Applicants allegedly have support for a vaccine that does not comprise an adjuvant in paragraphs 0084-0098 and Figure 4 (Applicant Remarks page 5, filed 6/27/2008). This example is silent about a carrier or adjuvant and fails to particularly point out a vaccine composition free of an adjuvant. Therefore, it is not clear if Applicants were in possession of the claimed invention.

Claims 13-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention is drawn to a vaccine and a method of prophylaxis and/or therapy of malaria comprising a recombinant MVA virus comprising at least one *Plasmodium*

falciparum MSP-1 protein or a fragment or **mutein** thereof, wherein the MSP-1 is reduced in its adenine and thymine (AT) content compared to the wild type sequence.

Applicant's disclosure lacks written description for all fragments and muteins of MSP-1 that retain the ability to induce a protective response against the target antigen. Applicant's disclosure also lacks written description for all MSP-1 with reduced AT content that can retain the ability to induce a protective response against the target antigen. The application provides some examples of virus constructs in Table 1. However Applicant's disclosure lacks written description of all fragments and muteins of MSP-1 and mutations in AT content that are therapeutic or provide protection against malaria.

The teachings in the art indicate that single amino acid changes can alter the antigenicity of the protein. See e.g., Riffkin et al., Gene 167:279-83, abstract (indicating that a single amino acid change between two proteins determines the ability of such proteins to bind to an antibody). The art also indicates that amino acid substitutions outside of an antigenic site in a protein may affect that ability of the protein to react with antibodies targeting the protein. Abaza et al., J Prot Chem 11:433-44. Thus, the art indicates that there is uncertainty in the ability of mutant versions of proteins to interact with antibodies directed against the original protein.

In view of the uncertainty in ability of mutants of MSP-1 to perform the required functions (the ability to provide protection against malaria), and the lack of any disclosure of other fragments or muteins of MSP-1 that perform such functions, the disclosure fails to provide adequate support for the claimed genus. The claims are therefore rejected as lacking adequate descriptive support for the claimed genus of fragments and muteins of MSP-1 and all MSP-1 mutations with reduced AT content.

The skilled artisan cannot envision the detailed structure of a genus of compounds that are contemplated in the invention. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 13-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the MSP-1 protein of *Plasmodium falciparum*, does not reasonably provide enablement for **all fragments and muteins of MSP-1 and all MSP-1 with reduced AT content**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claimed invention is drawn to a vaccine and a method of prophylaxis and/or therapy of malaria comprising a recombinant MVA virus comprising at least one *Plasmodium falciparum* MSP-1 protein or a fragment or **mutein** thereof, wherein the MSP-1 is reduced in its adenine and thymine (AT) content compared to the wild type sequence. It is not clear which muteins would retain the ability to be used for protection against malaria, or which muteins do not retain antigenicity of the parent proteins and would be useful for the ability to provide protection against malaria.

The first paragraph of 35 U.S.C. 112 states: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue

experimentation as requiring ingenuity beyond that to be expected of one of ordinary skill in the art (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). They include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a vaccine and a method of prophylaxis and/or therapy of malaria comprising a recombinant MVA virus comprising at least one *Plasmodium falciparum* MSP-1 protein or a fragment or **mutain** thereof, wherein the MSP-1 is reduced in its adenine and thymine (AT) content compared to the wild type sequence. The fragments of MSP-1 are selected from p83, p30, p38, p33, p19 and p42, or a combination thereof. The mutation comprises an amino acid addition, deletion, insertion, inversion and/or substitution of one or more amino acid and reduction of AT content compared to the wild type sequence.

The state of the prior art: The art further teaches that specific regions of the MSP-1 antigen enhances immunogenicity when expressed in a recombinant vaccinia vector as described by Yang et al. (Vaccine, 1997, Vol. 15, No. 12/13, pages 1303-1313). The art teaches that the complete MSP-1 of *Plasmodium falciparum* has been used to provide protection against challenge infection. The art teaches that specific mutations of the MSP-1 antigen are effective against neutralization of *Plasmodium falciparum* in a challenge. The art also teaches the MSP-1 is most effective in a neutralization assay when it comprises the signal and anchor regions with

the C-terminal MAP-1; however, it does not teach that all fragments and mutations of MSP-1 are effective in providing protection against malaria.

The amount of direction or guidance present and the presence or absence of working examples: Given the teachings of unpredictability in the art regarding the structural and functional differences in the MSP-1, detailed teachings are required in the disclosure to enable the full scope of the claims. Applicant's disclosure is limited to the examples on pages 11-14 of the amended specification. The only working examples are for MSP-1D-42 and MSP-1D-38/42, MSP-1D-83/30. Examples are provided for these fragments; however, no examples are provided for other fragments or mutations and the amount of reduction of AT content.

The breadth of the claims and the quantity of experimentation needed: Because the invention encompasses fragments and mutations of a surface protein and because the specification fails to provide guidance as to how to use the claimed method for all fragments and mutations other than the examples provided in the specification, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2 and 6-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (Nature Medicine, 1998, Vol. 4, No. 4, pages 397-402) in view of Yang et al. (Vaccine, 1997, Vol. 15, No. 12/13, pages 1303-1313), Kumar et al. (Immunology Letters, April 2002, Vol. 81, pages 13-24) and Bujard et al. (WO 98/14583, 1998).

The claimed invention is of record.

Schneider et al. (hereinafter Schneider) teaches a DNA plasmid vaccine with a recombinant modified vaccinia virus Ankara (MVA) expressing a *Plasmodium* antigen provided protection in mice against challenge (Abstract). Schneider teaches the vaccine composition was diluted in phosphate buffered saline (PBS) (carrier) before inoculating mice (*no adjuvant listed as relates to claim 20*) (page 401, 2nd column, end of 1st paragraph). Schneider teaches chimpanzee studies with MVA yielded very high levels of CD8+ T cells to a *Plasmodium falciparum* epitope (page 401, 1st column, 2nd paragraph). Schneider teaches expression of the plasmids was driven by a vaccinia promoter (page 401, 2nd column, 2nd paragraph) *as relates to claim 6*. Schneider teaches the expression plasmids were transfected into eukaryotic cells (page 401, 2nd column, 1st paragraph) *as relates to claim 11*.

Schneider does not teach using the MSP-1 protein, the *Plasmodium* strain 3D7, or a MSP-1 with reduced AT content.

Yang et al. teaches a recombinant vaccinia virus encoding a *Plasmodium falciparum* merozoite surface antigen (MSA1) (p. 1303, Abstract). A highly attenuated strain of vaccinia virus, Modified Vaccinia Ankara (MVA) was developed as an expression vector and shown to be equivalent to replication competent vaccinia virus in several vaccine models (p. 1311, last paragraph). The merozoite surface complex is processed into fragments, 30, 38 and 42 k Da (p.

1304, top of left column). Each gene was inserted into the thymidine kinase region of the vaccinia virus, under the control of the synthetic strong early/late promoter (p. 1303, Abstract). The effect of signal and anchor sequence on the biochemical processing and antibody response to the C-terminus region of the MSA1 is expressed by recombinant vaccinia virus (p. 1304, left column). BSC-1 cells (*eukaryotic host cells as relates to claim 11*) were transfected with a transfer vector, a recombinant vaccinia virus which encodes a *Plasmodium falciparum* MSA1 (p. 1305, left column). Insertion of the sequence, under transcriptional control of the promoter, provides a visual marker for identification (p. 1304, last paragraph). The MSA1 fragments contain the 108 bp region directly downstream from the signal sequence and an additional 2 bp on the 5' end of the C-terminal to preserve the reading frame (p. 1305, Table 1). The vaccinia virus thymidine kinase sequences flank the vaccinia genome (p. 1304, last paragraph). The virus containing the MSA1 was determined by SDS gel electrophoresis from the cell pellets and 50X concentrated supernatants (p. 1308, left column). Yang teaches a vaccine composition complete with Freund's adjuvant administered to monkeys, mice and rabbits in one vaccine or in two parts (p. 1304, 1st paragraph). Yang also teaches a vaccine composition that does not comprise adjuvant (p. 1307, 3rd paragraph) *as relates to claim 20*. The vaccines were administered to mice for the prophylaxis of malaria with the recombinant vaccinia virus vaccine (p. 1308, right column).

Kumar et al. (hereinafter Kumar) teaches about a DNA plasmid vaccine encoding the merozoite surface protein 1 (MSP-1) from the 3D7 strain of *Plasmodium falciparum* (Pf3D7) (Abstract) *as relates to claim 2*. Kumar also teaches about the construction of a vaccinia recombinant expressing MSP-1 (page 15, Section 2.2).

Bujard et al. (hereinafter Bujard) teaches a Malaria, *Plasmodium* species, which is stabilized by a process characterized by a reduction of the AT content (page 6, 3rd full paragraph). Bujard teaches vaccine carriers, viral carriers including vaccinia (page 13, 2nd full paragraph). Bujard also teaches processing fragments p83, p31, p36, p30 and p19 (page 15, last paragraph).

The claimed invention is drawn to a MVA virus (*as taught by Schneider*) comprising a *Plasmodium falciparum* merozoite surface protein MSP-1 protein or fragments or muteins thereof, from fragments p83, p30, p38, p33, p19, or p42 or a combination thereof (*as taught by Yang*), wherein the muteins comprise amino acid mutations and reduced AT content (*as taught by Bujard*).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use a surface protein such as MSP-1 in a DNA plasmid vaccine (*as taught by Schneider*) from a strain (3D7 *as taught by Kumar*) that is commercially available because Kumar teaches this vaccine composition elicited an antibody response in monkeys. It would have been obvious to a person of skill in the art to increase stability of the vaccine preparation as taught by Schneider by modifying the protein by reducing the AT content as taught by Bujard. The person of ordinary skill in the art would have been motivated to make a DNA vaccine comprising a surface protein because the references teach a successful vaccine comprising the surface protein of *Plasmodium falciparum*, and reasonably would have expected success because of the teachings of Schneider, Yang, Kumar and Bujard.

Response to Arguments

Applicants argue “one cannot extrapolate from vaccinia virus (the virus used by Yang) to MVA.” Yang teaches that MVA expression vector has been shown to be equivalent to vaccinia virus in vaccine models, however Yang does not teach a vaccine using MVA as a vector. Applicants also argue “It is well established in the art that MVA is a strongly attenuated vector which typically involves use of an adjuvant when using MVA as a vector.” Yang teaches a vaccine composition that does not comprise an adjuvant in an example of immunizing rabbits (p. 1307, 3rd paragraph). Schneider teaches using MVA as a vector for a malaria vaccine and does not teach using an adjuvant.

Claims 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (Nature Medicine, 1998, Vol. 4, No. 4, pages 397-402) in view of Yang et al. (Vaccine, 1997, Vol. 15, No. 12/13, pages 1303-1313), Kumar et al. (Immunology Letters, April 2002, Vol. 81, pages 13-24) and Bujard et al. (WO 98/14583, 1998) as applied to claims 1-2 and 6-21 above, and further in view of Sedegah et al. (Proceeding of the National Academy of Sciences USA, 1994, Vol. 91, No. 21, pages 9866-9870).

The new claims are drawn to a vaccine composition comprising a recombinant MVA virus comprising at least one *Plasmodium falciparum* MSP-1 protein and a pharmaceutically compatible carrier wherein the vaccine does not comprise an adjuvant.

The teaching of Schneider, Yang, Kumar and Bujard are described above however none of the references explicitly teaches a vaccine that does not comprise an adjuvant.

Sedegah et al. (hereinafter Sedegah) teaches an adjuvant-free malaria vaccine that produced high levels of antibodies and cytotoxic T lymphocytes in mice immunized with plasmid DNA encoding a *Plasmodium* protein (Abstract).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to make a malaria vaccine that does not comprise an adjuvant. The person of ordinary skill in the art would have been motivated to make an adjuvant-free vaccine because Sedegah teaches the vaccine is effective and obviates the requirement for adjuvants, and reasonably would have expected success because of the combined teachings of the references in view of Sedegah.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHARON HURT whose telephone number is 571-272-3334. The examiner can normally be reached on M, T, Th, F 8:00 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sharon Hurt/
Examiner, Art Unit 1648

June 22, 2009

/Dong Jiang/
Primary Examiner, Art Unit 1646